Pretesting chemical additives

Assuring the safety of environmental additives is a heavy moral, economic, and technical burden on the sponsors of new products. The Delaney amendments of 1958 added the legal requirement that food additives be tested in advance of their sale. The definition of safety was left to administrative judgment except for the famous clause that no additive is legally safe if "it is found to induce cancer when ingested by man or animal."

Until the cyclamate incident of recent months, the cancer clause and the concept of zero tolerance did seem to be incongruous with a scientifically precise approach. However, they impelled Secretary Finch to take the economically distressing but prudent and necessary step of banning cyclamate from general use. Now he has relaxed the ban in response to criticisms that cyclamate has not yet been proved to have any harmful effect in man. "What significance can there be in finding bladder cancers in rats fed 50 times the levels recommended for human intake!"

This question reflects our perplexities in finding any way whatsoever to pretest the chronic hazards of an additive, short of a large-scale trial on an unknowing human population, which would have many of its own difficulties to impede scientific rigor.

Consumers represent a very wide spectrum of variation in genetic constitution, age, health, pregnancy, diet, exposure to drugs and other additives—all factors that could reasonably influence their response to a carcinogenic insult. For example, many compounds are detoxicated by conjugation with glucuronic acid in the liver, a process that may be impaired by liver disease, swamped by overload with other ligands, or reversed by glucuronidase activity in the bladder.

Even in genetically pure strains of mice, bred in carefully controlled environments, only a proportion will respond to intermediate doses of known carcinogens within their short lifetimes.

Furthermore, industrial carcinogens like 2-naphthylamine may have latencies of 10 to 20 years before bladder cancer appears in exposed workers. We are fortunate to have animal models for this carcinogen, by the *ad hoc* procedure of implanting its *N*-hydroxy metabolite directly in the urinary bladder.

It would be held a catastrophe if a hundred innocent U.S. consumers a year were carcinogenized by a food additive they could happily live without. Unfortunately, even the most stringent animal tests we can practically devise will not reliably detect such a hazard. Surely we do not dare ignore the positive warning when 50% of a small group of animals show bladder cancer at any dose. Blind faith that the dose-response curve in man has a no-effect threshold at some intermediate level is as unscientific as the literal interpretation of "zero tolerance." A practical one is "do not intentionally eat, or cause others to eat, suspected carcinogens until they are proved otherwise."

Or, at least, publish the standard of tolerance of the expected incidence of human cancer.

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